

The use of animal models in homeopathic research – a review of 2010–2014 PubMed indexed papers



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Background: In the 1990s, a study was performed on the effects of highly diluted thyroxine on frog metamorphosis. This model represented one of the most discussed examples of the biological effects of high dilutions over the next two decades. In 2010, another critical conceptual review of the use of animal models in homeopathy and high-dilution research was published. The main contribution of these studies was the elucidation of the biological features and phenomenology of the effects of high dilutions on living systems, representing an important step forward in our understanding of the mechanisms of action of homeopathic medicines.

Methods: We performed a further review of this line of investigation using the same methods. Fifty-three articles that were indexed in the PubMed database and used 12 different animal species were systematically evaluated. Only a fraction of the studies (29/53) reported herein were performed with “ultra high” dilutions. The other studies were performed with dilutions in ranges below 10^{-23} (14/53 articles) or commercial complexes (10/53 articles).

Results: Only two articles reported negative results; both used *in vivo* protocols to test commercial complexes, one in fish and one in bees. The quality of the employed techniques improved in 2010–2014 compared with the studies that were reviewed previously in 2010, with the inclusion of more ethically refined protocols, including *in vitro* primary cell cultures and *ex vivo* studies (10/53 articles), often with three or more replicates and analyses of epigenetic mechanisms that were previously unknown in 2010.

Conclusion: In our updated review of the past 5 years, we found further demonstrations of the biological effects of homeopathy using more refined animal models and *in vitro* techniques. *Homeopathy* (2015) 104, 283–291.

Keywords: Homeopathy; High dilutions; Animal models; Review

Introduction

In 1994, a chapter was published in the book *Ultra High Dilution: Physiology and Physics*,¹ describing in detail the steps of a protocol to study the effects of highly diluted thyroxine on frog metamorphosis. This model represented one of the most discussed examples of the biological effects of high dilutions over the next two decades. In 2010, another critical conceptual review of animal models in homeopathy and high-dilution research was published

that evaluated this and other animal models.² The main contribution of these studies was the elucidation of the biological features and phenomenology of the effects of high dilutions on living systems, representing an important step forward in our understanding of the mechanisms of action of homeopathic medicines.

The multiple animal models that are found in the literature between 1999 and 2009 presented adequate methodology that provided biological evidence of the homeopathic principle of *similarity*, mainly regarding the modulation of parasite-host interactions and recovery of a “steady-state” in the challenged hosts after treatment with homeopathic (or isopathic) highly diluted substances.² A further analysis of these previous studies indicated the necessity to develop new and innovative experimental designs.

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In this mini-review, we selected articles from the PubMed database that were published in 2010–2014 and analyzed the methodological quality of each selected paper and its contribution to our understanding of homeopathic and isopathic phenomenology.

Methods

According to the methodology that was previously reported in the 2010 review,² we searched for articles only in the PubMed database from January 2010 to December 2014 using a combination of the following keywords: “animal,” “mice,” “rats,” “homeopathic,” or “homeopathy.” Only original, full-text, English-language articles that reported experimental studies that used animal models and were available on-line were considered for this review. *In vitro* studies that used animal primary cell cultures were also included. Veterinary clinical trials, theses, reviews, and *in vitro* studies that used human cell lines were not considered.

Fifty-three (53) articles were selected for this review. The assessment of the methodological quality was performed according to the previous review.² Aspects of the conceptual and experimental design were evaluated according to the following criteria: (i) convergence of data toward a consistent conclusion, (ii) protocol details and innovative experimental approach, and (iii) results derived from studies that used dilutions above or below Avogadro's number.

Results

We systematically evaluated 53 articles that were indexed in the PubMed database. These articles reported results that were obtained from 12 different animal species. Only a fraction of the studies (29/53) reported herein were performed with “ultra high” dilutions. The other studies were performed with dilutions in the range below 10^{-23} (14/53 articles) or commercial complexes (10/53 articles). Only two studies reported negative results using *in vivo* protocols. Both tested commercial complexes, one in fish and the other in bees. We found that the quality of the employed techniques improved substantially compared with the studies that were reported in 2010, with the inclusion of more refined protocols and use of good laboratory practice, species-pathogen-free animals, *in vitro* primary cell cultures, and *ex vivo* protocols (10/53 articles), often with three or more replicates and analyses of epigenetic mechanisms.

With regard to the methodological quality of the samples and statistical methods, only 43% of the studies were performed in a blinded manner, and 82% were performed with randomized samples.

Considering only the studies that included high potencies (above Avogadro's number), 11/29 were performed in blind and 18/29 were not, but all of them presented positive results, being 03 studies with positive results only for potencies below 9c. Also, among them 13/29 mentioned

some sample randomization and 06/29 mentioned multiple assay replications.

The control standard was defined as vehicle or untreated animals, but 25/53 articles included a positive control (i.e., a non-homeopathic substance). The statistical analyses included both parametric and nonparametric methods, but only three studies reported the use of Bartlett's test to verify homoscedasticity of the employed samples. Interestingly, three or more replicates were reported for assays that were performed in fish (4/53), mice (5/53), and nonhuman primates (1/53). One study that was performed in fish used an n of 1200, and one study reported an two experiments that were designed according to good laboratory practice. A summary of the selected papers is presented in Table 1.

Discussion

Eighty-nine articles from 1999 to 2009 were selected from PubMed database in the first review that was published in 2010.² In the same issue, a bibliometric study was made considering only the very high dilutions.⁵⁴ In the present mini-review, 53 articles were selected from 2010 to 2014, using the same search criteria (only PubMed), demonstrating regularity in research on homeopathy using animal models. Again, a new bibliometric analysis was made this issue.⁵⁵

In the 2010 review, the most important conclusions were the following: (i) the methodological quality of the majority of the papers was adequate, in which blinded procedures and the randomization of samples were considered, (ii) convergence between the experimental results and respective *materia medica* pointed to the plausibility of the *similia principle*, (iii) most of the experimental studies on homeopathy and isopathy were useful for understanding complex biological phenomena, such as parasite-host relationships, and (iv) most of the studies pointed to the ability of high dilutions to recover a steady state in the organism to control levels after they were challenged with aggressive stimuli.

With regard to methodological quality in the present review, approximately 43% of the studies were performed in a blinded manner, and 82% used randomized samples. The control standard was defined as vehicle or untreated animals. Twenty-five of the 53 articles also included a positive control (i.e., a known non-homeopathic substance). The statistical analyses included both parametric and nonparametric methods, but only three studies reported the use of Bartlett's test to verify homoscedasticity of the employed samples. These data indicate some fragility in the standard methods, mainly related to the low frequency of blinded procedures. Interestingly, however, there was no correlation between methods and results. Moreover, three or more replicates were seen in assays that were performed in fish (4/53), mice (5/53), and nonhuman primates (1/53). One study that was performed in fish had an n of 1200, and two studies were performed according to good laboratory practice guidelines. Thus, some strengths can also be seen.

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